confusion with entities such as lymphoma, sarcoid or, among homosexual men, cytomegalovirus infection or *Pneumocystis carinii* pneumonia, the clinical diagnostic criteria we suggest may prove useful.[16]

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Acute Renal Failure Following Repeated Streptokinase Therapy for Pulmonary Embolism

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PREVIOUS REVIEWS[1,2] have described the benefits and risks of administering fibrinolytic agents to bring about clot dissolution in both arterial and venous disease. As activators of the conversion of plasminogen to plasmin, these agents produce major side effects that include varying degrees of hemorrhage. Other complications, particularly with the use of streptokinase, are pyrogenic and allergic reactions, including anaphylaxis.[3] In this report we describe the case of a patient in whom a pyrogenic reaction and acute renal failure developed after he received streptokinase on the second of two occasions for pulmonary embolism.

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Report of a Case

A 38-year-old man was admitted to our hospital because of the recent onset of chest pain. Further history disclosed a contusion of the right calf that was followed by several episodes of localized pain and swelling. On the day of admission, his chest pain and associated symptoms were typical of angina pectoris. On examination in the coronary care unit, the respiratory rate was 40 per minute, the pulse was 88 per minute and the blood pressure was 100/88 mm of mercury. There was no jugular venous distention. The lungs were clear to auscultation. The point of maximal cardiac impulse was not displaced, the first and second heart sounds were normal and a fourth heart sound was present at the apex. No murmurs or friction rubs were audible. Peripheral pulses were normal. The lower extremities were not tender and there was no evidence of edema, erythema or localized calor. The remainder of the examination findings were unremarkable.

An electrocardiogram showed normal sinus rhythm, pronounced left axis deviation, deeply inverted T waves in leads V_1 through V_4, and deep S waves in leads V_5 and V_6. A portable chest x-ray study showed no abnormalities. The hemogram, sedimentation rate, serum urea nitrogen, serum creatinine and analysis of urine gave normal values. An arterial blood gas determination made while the patient was breathing room air showed that the partial pressure of oxygen (Pao_2) was 71 mm of mercury, the partial pressure of carbon dioxide ($Paco_2$) was 28 mm of mercury and the pH was 7.47. Creatine kinase was 107 IU per liter (normal, 225 or less), lactic dehydrogenase was 248 IU per liter (normal, 200 or less) and aspartate aminotransferase (formerly, SGOT) was 28 IU per liter (normal, 41 or less). Serial cardiac enzyme determinations did not suggest an acute myocardial infarction.

During the first two hospital days, angina-like chest pain continued to recur but was relieved by the sublingual use of nitroglycerin. On the third hospital day a cardiac catheterization was done. All right heart pressures were moderately elevated. The pulmonary artery pressure was 59/27 mm of mercury, with a mean pressure of 34 mm of mercury. Pulmonary angiography showed large embolic filling defects in the right and left proximal pulmonary arteries with smaller filling defects in the branch vessels supplying the right and left upper lobes and the left lower lobe. Findings on left ventriculography and coronary arteriography were normal. Streptokinase therapy was begun, with a loading dose of 250,000 units and an hourly infusion of 100,000 units. After two hours there was bleeding from the femoral arterial and venous catheterization sites that could not be controlled. Administration of the drug was discontinued, and continuous infusion of heparin was begun to maintain the partial thromboplastin time in the range of 1½ to 2½ times the control values.

On the 11th hospital day, pain in the patient's right calf, acute chest pain and dyspnea recurred. There was a palpable tender cord in the right popliteal area. An

arterial blood gas determination while the patient was breathing room air showed a Pao_2 of 62 mm of mercury, a $Paco_2$ of 30 mm of mercury and a pH of 7.56. Electrocardiograms continued to show a right ventricular strain pattern. Because of evidence for recurrent pulmonary emboli while receiving heparin and the unavailability of urokinase, streptokinase therapy was reinstituted. Four hours after resumption of the drug, the patient had diffuse myalgias, a fever developed to 40.6°C (105°F) and he had rigors. He had no rash or bronchospasm and was never hypotensive. Coagulation measurements were made and were not significantly different from their control values. Because of no apparent "lytic effect" and the severe febrile response, streptokinase therapy was discontinued and continuous infusion of heparin was resumed at a higher dose. During the next 15 hours the patient was oliguric. No other drug was being administered.

The serum creatinine level rose from the admission value of 1.3 mg per dl to 2.8 mg per dl. The initial serum urea nitrogen level was 28 mg per dl and the leukocyte count rose to 27,000 per cu mm, with a normal differential count and no eosinophils. Multiple blood cultures grew no organisms. The serum creatine kinase value was initially elevated to 443 IU per liter but returned to normal on later tests. The uric acid level was 5.4 mg per dl and did not rise on further measurements. Urine analysis showed many leukocytes and fine granular casts, few hyaline casts and no erythrocytes or erythrocyte casts. Dipstik tests showed 3+ protein and 1+ occult blood. No eosinophils were seen on Wright's stain of the urine. Other studies of the urine showed 13 mEq per liter of sodium, a creatinine level of 26 mg per dl and an osmolality of 279 milliosmole (mosm) per kg of water (normal, 50 to 800). Fractional excretion of sodium was 6.9 percent. During the first 24 hours of his renal failure, the serum creatinine and urea nitrogen tests reached their highest values of 4.8 mg per dl and 57 mg per dl, respectively.

Over the next five days the patient's oliguria resolved. By the 13th hospital day the serum creatinine level was 1.2 mg per dl. The highest serum potassium level reached was 5.8 mEq per liter. Serum calcium concentration fluctuated within a range of 7.7 and 8.5 mg per dl. After a long additional time in hospital, the patient was discharged in good condition on a regimen of oral anticoagulants. Subsequently, renal function findings remained in the normal range with no recurrence of renal impairment.

Discussion

This is not the first instance of acute renal failure being related to the use of streptokinase. Rieben and co-workers[4] reported the case of a 65-year-old man in whom livedo reticularis developed two days after beginning thrombolytic therapy with streptokinase. Following this, necrosis on one foot and acute renal failure developed. The patient died and an autopsy showed severe ulcerative atherosclerosis of the aorta with cholesterol embolization to numerous organs, particularly the kidneys. The close timing between streptokinase infusion and the subsequent clinical findings led the authors to conclude that the thrombolytic therapy contributed to acute diffuse embolization by dissolving the protective thrombi over the ulcerative atheromatous plaques.

A case somewhat similar to ours was reported by Spangen and colleagues[5] in which a 50-year-old man was given streptokinase because of deep venous thrombosis that was progressing despite heparin therapy. Four days after discontinuing treatment with streptokinase, back pain developed, along with glycosuria, hypo-osmolality of the urine and a slight rise in the serum creatinine level. A radionuclide renal scan showed normal glomerular uptake but bilateral postglomerular obstruction. In the ensuing week, his symptoms and laboratory abnormalities resolved and a follow-up renal scan showed no abnormalities. The authors attributed his renal dysfunction to a nonspecific immune reaction.

The precise cause for our patient's acute renal failure was not clear. A biopsy of a kidney could have provided important information but it would have required discontinuation of anticoagulant drugs. Even without a tissue diagnosis, the acute renal failure, as observed in this case, would suggest several possible causes.

Having undergone a cardiac catheterization, the patient could have had a toxic nephropathy due to iodinated radiographic contrast material. However, eight days elapsed before there was any sign of renal insufficiency; thus, this possibility is untenable. Prerenal azotemia might also be considered, but the laboratory results and clinical course following the onset of acute renal failure make this diagnosis unlikely. An attractive hypothesis is that streptococcal antigens precipitated an acute glomerulonephritis. Indeed, an eight-day "latent period" had elapsed from the time of the first streptococcal antigen exposure. In contrast to our patient, however, most persons in whom poststreptococcal glomerulonephritis develops have only vague constitutional symptoms at the time of onset, and fever is unusual.[6] Furthermore, the fractional excretion of sodium militates against the diagnosis of glomerulonephritis.[7] Because the events and laboratory results are more representative of an acute tubulointerstitial process, at least two other causes were considered.

The rigors and high temperature observed in this patient could have caused rhabdomyolysis and acute renal failure. In favor of this diagnosis was the (mildly) elevated creatine kinase level, urine positive for occult blood with no erythrocytes found on microscopic examination, the rapid rise in serum creatinine level and the presence of mild hypocalcemia. Pigmented granular casts were not seen, however, and the serum values for uric acid and potassium were not raised. Nevertheless, myoglobinuric renal failure has been reported to occur under similar clinical circumstances with only modest elevations of serum creatine kinase.[8]

Having been immunologically sensitized with the

first exposure to streptokinase, this patient very likely had a hypersensitivity reaction associated with the streptococcal antigen. With the close relationship to oliguria, an acute hypersensitivity-induced interstitial nephritis and renal failure may be the diagnosis most in keeping with this case. Although the presence of eosinophils in the blood or urine was not observed, this finding is not necessarily required for the diagnosis.[9] As is typical in most cases of acute interstitial nephritis, renal dysfunction resolved after removal of the offending agent.

Summary

Streptokinase may be responsible for acute renal failure on the basis of a hypersensitivity reaction resulting in either an acute interstitial nephropathy or renal failure due to myoglobinuria from nontraumatic rhabdomyolysis. Atheroembolic renal failure may be an operative mechanism in older patients. Given appropriate indications and in the absence of contraindications, there is no reason to deny a patient an initial course of streptokinase. Based on our experience with repeated streptokinase therapy, we would recommend the use of urokinase if a thrombolytic agent is to be used in the context of recent streptokinase administration. Otherwise, alternative measures (for example, vena caval umbrella or clipping) may be a better choice for the management of ongoing pulmonary thromboembolic disease.

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